REMARKS

Claims 1, 3, 4, 6, and 9-11 have been amended. Claims 2 and 7 have been canceled without prejudice. Support for the amendments to the claims can be found throughout the specification including paragraphs [0016]-[0019], [0025], [0030]-[0033], [0050], [0051], and [0053]. Applicants submit that no new matter has been added via these amendments to the claims.

OBJECTION

The specification has been objected to because the Abstract of the Disclosure did not commence on a separate sheet. The Abstract of the Disclosure has been presented on a separate sheet as required. Accordingly, the objection is moot and withdrawal is requested.

35 USC § 112, ¶ 2

Claims 2-5, 7, and 9-12 have been rejected as being indefinite. In the view of the Patent Office, the use of the term "form" is confusing because claims 2 and 7 read "as if both [the injectable and oral calcium] forms were present in the same composition at the same time," and "claim 4 recites a completely different 'form' of the calcium than is referred to in claims 2 and 7." (Paper No. 20070816, at 3-4.)

Claims 2 and 7 have been canceled without prejudice and claim 4 has been amended to delete the term "form". Thus, the rejection is moot with regard to claims 2, 4, and 7. In addition, claims 1 and 6, as amended, recite that part of the calcium is in "injectable form and the other part is in oral form…." (The remaining rejected claims now ultimately depend from either claim 1 or claim 6.)

The Patent Office has apparently determined that the injectable form and oral form of calcium are part of a single composition. Claim 1, however, recites a "combination comprising calcium, injectable magnesium, and an active ingredient which releases oxalate during its metabolism." Likewise, claim 6 recites "administering to a patient a combination of calcium and magnesium…." Thus, both independent claims recite a combination. It is this combination that includes calcium in an "injectable form" and an "oral form." Certainly, a skilled artisan would readily ascertain that the claimed combinations and methods include more than one form of calcium that are administered via separate compositions.

Accordingly, it is submitted that the recitations of the claims are clear and definite. Withdrawal of the rejection as it applies to claims 3, 5, and 9-12 is requested.

35 U.S.C. § 102(b)

Claims 1, 3, 6, and 8 have been rejected as anticipated by Grolleau et al. Applicants respectfully traverse this rejection.

Because claims 2 and 7 have not been rejected as anticipated by Grolleau et al., the Office has acknowledged that these claims are novel over this reference. Claims 1 and 6 (from which claims 3 and 8, respectively, depend) have been amended to incorporate the recitations of claims 2 and 7, respectively. Therefore, the rejection is moot. Withdrawal is requested.

Claims 1, 3, 4, 6, and 8 have been rejected as anticipated by Lainè-Cessac et al. Applicants respectfully traverse this rejection.

Because, claims 2 and 7 have not been rejected as anticipated by Lainè-Cessac et al., the Office has acknowledged

that these claims are novel over this reference. As discussed above, claims 1 and 6 (from which claims 3-4 and claim 8, respectively, depend) have been amended to incorporate the recitations of claims 2 and 7, respectively. Thus, the rejection is moot. Withdrawal is requested.

35 U.S.C. § 103(a)

Claims 1-12 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Lainè-Cessac et al. in view of U.S. Patent Application Publication 2001/0018082 (the "'082 application") and further in view of U.S. Patent 5,767,149 (the "'149 patent"). Applicants respectfully traverse.

The Patent Office has alleged that Lainè-Cessac et al. discloses that the "anticancer agent (line 5) oxaliplatin-induced neurotoxicity (1st sentence) can be dramatically improved after simultaneous (patient F/49 in table) or post-injection (patient F/59 in table) administration of calcium and magnesium. Patients were intravenously administered a mixture of calcium gluconate and magnesium sulfate (1st sentence below table as noted above)." (Paper 20078016, at 5-6.) The Patent Office has acknowledged that Lainè-Cessac et al. differs from the claimed invention in that it "does not teach … the administration of both the calcium in oral and parenteral form…." (*Id.*, at 6.)

To remedy this deficiency, the Patent Office has cited the '082 application, which allegedly discloses "an oral calcium supplement in the form of an effervescent calcium supplement (title)," and the '149 patent, which in Example B-11, is alleged to disclose "'in use, one bag of [an ascorbic acid] product is dissolved in about 300-500 ml of water, and the solution is favorably useable as an intubation nutrient directed to oral and parenteral administration to the nasal cavity, stomach and intestine." (*Id.*)

Based on the foregoing, the Patent Office has determined that "it would have been obvious to one of ordinary skill in the art at the time the invention was made that the calcium 'part' of the composition could simultaneously be delivered orally and parenterally since [the '149 patent] makes it clear that a well-known supplement such as ascorbic acid can be administered in both oral and parenteral form." (*Id.*) Applicants respectfully disagree.

Lainè-Cessac et al. discloses that the acute neurotoxic effects of oxaliplastin administration can be dramatically improved by intravenous administration of calcium gluconate and magnesium sulfate immediately after onset of the neurotoxic effects. Lainè-Cessac et al. is silent as to oral administration of calcium. The '082 application discloses an effervescent calcium dietary supplement, preferably an effervescent beverage, which delivers an effective amount of calcium citrate malate. The '082 application, however, makes no mention of oxalate therapy or more particularly to preventing or treating nuerotoxicity caused by such therapy.

The '149 patent discloses a particular ascorbic acid analog. The rejection points to Example B-11, in which a single composition is "favorably usable as an intubation nutrient directed to oral and parenteral administration to the nasal cavity, stomach and intestine." (Col. 18, lines 28-30.) This example, and the '149 patent as a whole for that matter, are silent with regard to the administration of calcium in any form. Accordingly, the '149 patent provides nothing to remedy the deficiencies of the combination of Lainè-Cessac et al. and the '082 application.

In sum, the collective teachings of the cited prior art references do not establish *prima facie* obviousness.

In addition, the claimed invention is nonobvious because it solves a problem that the prior art did not

recognize. Inventions based on application of known solutions to previously unknown problems have been held to be non-obvious and patentable.

Before the present Applicants' invention, it was believed that the neurotoxic effects of oxaliplatin appeared only during or immediately after infusion of the oxaliplatin. In other words, the late-onset of neurotoxic effects was not a concern. Consequently, and as borne out by the cited prior art itself, therapies for treating these neurotoxic effects focused exclusively on immediate treatment. *See, e.g.*, Lainè-Cessac et al. However, this belief turned out to be mistaken. As Applicants explain in paragraph [0053] of the present specification, "[i]n some cases, it is found necessary to continue with the administration of Ca in order to reduce the risk of onset of neurological manifestations at a distance from the administration of oxaliplatin." In solving the problem with a combination of injectable and oral administration of calcium, Applicant's claimed invention thus produces unexpected results in treating the previously unappreciated late-onset neurological side effects of oxaliplatin.

In *Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45 (1923), the Supreme Court ruled that the first recognition of the existence of a problem is not obvious and involves discovery and invention. In *Eibel Process*, the patent in question was directed to an improvement in a standard paper making machine. In the machine, a stream of pulp stock flowed onto a moving wire cloth in order to drain water out of the stock over the 30 foot-length of the cloth. The prior art taught that increasing the speed of the wire cloth increased productivity, but at the same time, caused the defective paper with poor quality. The patentee's contribution was to increase the pitch of the wire cloth in order to use gravity to increase

the rate of flow of pulp on the wire cloth to equal the rate of flow of the wire cloth itself. The Supreme Court held thusly:

> It was the discovery of the source not before known and application of the remedy for which *Eibel* was entitled to be rewarded in his Patent. . . . We cannot agree with the Circuit Court of Appeals that the causal connection between the unequal speeds of the stock and the wire, and the disturbance and rippling of the stock, and between the latter and the defective quality of the paper in high speeds of the machine was so obvious that perception of it did not involve discovery which will support a patent.

Eibel Process, at 68.

Similarly, in *In re Nomiya*, 509 F.2d 566, 184 USPQ 607 (C.C.P.A. 1975), the Court of Customs and Patent Appeals (CCPA) held that the doctrine established by the Supreme Court in *Eibel Process* also applies when the inventor was the first to encounter or perceive a problem even though he uses known or obvious means of solving it. *Nomiya* dealt with an improvement in an insulated gate-type field effect transistor (IGFET) for use as a switching device in memory circuits having very low capacitance. The CCPA reasoned thusly:

> If, as appellants claim, there is no evidence of record that a person of ordinary skill in the art at the time of appellants' invention would have expected the problem in the IGFET to exist at all, it is not proper to conclude that the invention which solves this problem, which is claimed as an improvement of the device, would have been obvious to that hypothetical person of ordinary skill in the art. The significance of evidence that a problem was known in the art is, of course, that knowledge of a problem provides a reason or motivation for workers in the art to apply their skill to its solution. Logically, the instant situation is one step removed from the circumstances illustrated by *Eibel Process*

> *Co. v. Minnesota & Ontario Paper Co.* … where *the problem* of rippling in paper produced on Fourdrinier paper-making machines at high speed *was known*, but the source of the problem was not.

Nomiya, 509 F.2d at 572, 184 USPQ at 612-613.

Accordingly, withdrawal of the rejection is requested.

CONCLUSION

As it is believed that the objection and rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he telephone Applicants' attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Applicants' Deposit Account No. 12-1095 therefor.

Dated: November 28, 2007

Respectfully submitted,

By _____
Stephen J. Brown
Registration No.: 43,519
LERNER, DAVID, LITTENBERG,
KRUMHOLZ & MENTLIK, LLP
600 South Avenue West
Westfield, New Jersey 07090
(908) 654-5000
Attorney for Applicant

823467_1.DOC